COPY

No. COX 00-031
May 05, 2000

Bulletin for VIOXX:
New PIRs Relative to VIOXX GI Outcomes Research Study

TO:

All field personnel with responsibility for VIOXX® Action Required

PURPOSE:

In response to recent published reports about VIOXX, Medical Services has been working to provide a rapid response to physicians unsolicited requests for information.

Effective Monday morning, May 8, a new PIR that will include incidence rate of MIs with VIOXX will be available from Medical Services via an interactive voice response (IVR) same day fax service to address your customers concerns. As a result of this PIR being available from Medical Services via same day fax to your customers, you may no longer print and distribute the PIR provided to you via Bulletin COX00-019.

OVERVIEW:

In response to recent published reports about VIOXX, on May 1, 2000, we provided you with an approved verbal response to use to address customers questions around the incidence rate of MIs on patients taking VIOXX via Bulletin COX00-029. Follow the directions on Bulletin COX00-029 for using that information. Now that you have this information to respond to questions from your customers (verbally) and the new PIR with incidence rate of MIs is available from Medical Services via same day fax, you may no longer distribute the printable PIR provided to you via Bulletin COX00-19 to your customers.

In addition, Medical Services has developed a PIR to assist physicians in responding to patients' questions that arise as a result of the news coverage. This PIR is also available from Medical Services via the IVR same day fax service.

ACTION REQUIRED:

- Immediately discontinue distribution of the printable PIR provided to you via Bulletin COX00-019.
- Review the Obstacle Responses around the incidence rate of MIs with VIOXX provided to you via Bulletin COX00-029.
- When a physician requests information on the VIOXX GI outcomes research trial or has a patient with concerns regarding COX2 inhibitors, you may submit a request for a PIR by simply calling 877-372-7064 (8:00 A.M. to 10:00 P.M. EST) that will link you to an interactive voice response service for the Medical Services PIR request line. A touch tone phone must be used to provide the following information:
  - Your 8 digit RDT
  - Physician's 5 digit ZIP code
  - Physician's full name and professional degree
  - Physician's full mailing address
  - Physician's phone number
  - Physician's FAX number

PLAINTIFF'S EXHIBIT

Exhibit A - Part 9

- Select one or both of the requested PIRs entitled:
  - A brief summary of VIGOR (Note – This is the new PIR which includes incidence rate of MIs with VIOXX that replaces the printable PIR previously provided to you.)
  - Data to address a patient's concerns about COX2 inhibitors.

- You should only call 877-372-4568 (8:00 A.M. to 8:00 P.M. EST), if you experience difficulty with the interactive voice response system. A staff member will be available to help you.

IF YOU HAVE ANY QUESTIONS CONCERNING THIS BULLETIN, PLEASE CONTACT THE MERCK NATIONAL SERVICE CENTER AT 1-800-NSC-MERCK.

No. COX 00-032
May 08, 2000

REVISED Bulletin for VIOXX:
New PIRs Relative to VIOXX GI Outcomes Research Study

TO:

All field personnel with responsibility for VIOXX®(rofecoxib). Action Required

PURPOSE:

This bulletin replaces COX 00-031. The phone number for the Medical Services PIR FAX Request Line has not changed. The bulletin was updated to reflect the new technical (IVR) support number which you should call if you are having difficulty with the interactive voice response system.

In response to recent published reports about VIOXX, Medical Services has been working to provide a rapid response to physicians unsolicited requests for information.

Effective Monday morning, May 8, a new PIR that will include incidence rate of MIs with VIOXX will be available from Medical Services via an interactive voice response (IVR) same day fax service to address your customers concerns. As a result of this PIR being available from Medical Services via same day fax to your customers, you may no longer print and distribute the PIR provided to you via Bulletin COX00-019.

OVERVIEW:

In response to recent published reports about VIOXX, on May 1, 2000, we provided you with an approved verbal response to use to address customers questions around the incidence rate of MIs on patients taking VIOXX via Bulletin COX00-029. Follow the directions on Bulletin COX00-029 for using that information. Now that you have this information to respond to questions from your customers (verbally) and the new PIR with incidence rate of MIs is available from Medical Services via same day fax, you may no longer distribute the printable PIR provided to you via Bulletin COX00-19 to your customers.

In addition, Medical Services has developed a PIR to assist physicians in responding to patients' questions that arise as a result of the news coverage. This PIR is also available from Medical Services via the IVR same day fax service.

ACTION REQUIRED:

- **Immediately discontinue distribution of the printable PIR provided to you via Bulletin COX00-019.**
- Review the Obstacle Responses around the incidence rate of MIs with VIOXX provided to you via Bulletin COX00-029.
- When a physician requests information on the VIOXX GI outcomes research trial or has a patient with concerns regarding COX2 inhibitors, you may submit a request for a PIR by simply calling the **Medical Services PIR Request Line toll free at 877-372-7064 (8:00 A.M. to 10:00 P.M. EST).** Since this line is an interactive voice response system, a touch tone phone must be used to provide the following information:
  - Your 8 digit RDT
  - Physician's 5 digit ZIP code

Exhibit A - Part 3

- Physician's full name and professional degree
- Physician's full mailing address
- Physician's phone number with area code
- Physician's FAX number with area code
- Select one or both of the requested PIRs entitled:
  - A brief summary of VIGOR (Note – This is the new PIR which includes incidence rate of MIs with VIOXX that replaces the printable PIR previously provided to you.)
  - Data to address a patient's concerns about COX2 inhibitors
- These two PIRs will be faxed directly to the requesting physician's office as a 'nonpersonalized letter'. You will need to leave a copy of the circular for VIOXX with the physician.

- If you experience difficulty with the interactive voice response system, please call the toll free phone number established only for this process, IVR help line at 888-721-7204 (8:00 A.M. to 8:00 P.M. EST).. A staff member will be available to help you.

- For other questions concerning VIOXX requested by your physician, please follow the usual PIR procedures. These PIRs will continue to be 'personalized' with the physician's name, and you will receive a copy, as per usual PIR procedures. (See Policy 104)

IF YOU HAVE ANY QUESTIONS CONCERNING THIS BULLETIN, PLEASE CONTACT THE MERCK NATIONAL SERVICE CENTER AT 1-800-NSC-MERCK.

No. COX 01-007
Feb 09, 2001

COPY

Bulletin for VIOXX®:
FDA Arthritis Advisory Committee Meeting for VIOXX®

TO:

All field personnel with responsibility for VIOXX®
National Account Executives
and Customer Managers (All Segments)

Action Required
Background Information

DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS ADVISORY COMMITTEE (ADVISORY COMMITTEE) REVIEW OR THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.

Introduction:

As previously communicated in June 2000, Merck submitted a supplemental NDA for VIOXX based upon the VIOXX GI Outcomes Research study (VIGOR). In this study, VIOXX 50mg daily significantly reduced the risk of serious gastrointestinal side effects by 54% vs. naproxen 1000mg daily. On Thursday, Feb 8, Merck and the FDA reviewed the study with the FDA's Arthritis Advisory Committee.

The purpose of this bulletin is to provide you with important, updated background information based on the results of this meeting and actions required by you.

Action Required:

1. Stay focused on the EFFICACY messages for VIOXX
2. Utilize the PIR system to respond to unsolicited physician inquiries
3. Review the updated background Q&A
4. Review the updated obstacles and responses for your physicians
5. Do not initiate discussions or respond to questions, except as outlined below

Stay Focused on Efficacy

It is critical that we remain focused on the 1S HI NSAID and HI COXIB messages for VIOXX with our targeted physicians. As discussed at your 1S District Meetings, both the OA efficacy data and the new acute pain narcotic efficacy data for VIOXX will continue to solidify the efficacy perception of VIOXX. Use the new core visual aid for VIOXX and the

Exhibit

PLAINTIFF'S EXHIBIT

OA Efficacy Stock Bottle Challenge program to challenge physicians to gain experience with the 24 hour efficacy of VIOXX.

Physician Inquiries:

In response to unsolicited requests for information regarding VIGOR, Medical Services will make a personalized, faxable PIR available for your customers within 24 hours. In addition, for those customers who request additional information, a separate, more comprehensive PIR packet can be Federal Expressed within 2 days.

Medical Services has made arrangements to extend the hours for the PIR hotline. Representatives should submit unsolicited PIR requests by either telephone or fax options from 2/9 through 2/23 by calling the PIR hotline 800MERCK66 (800-637-2566) during extended hours of 8:30 am to 6:30pm ET. During these hours, a staff member will verbally request the following information from you to process the PIR request from the HCP [After this time, the usual method options of INSIGHT, PIR hotline (800MERCK 66 – hours: 8:30 – 4:30pm ET) and fax can be followed].

Faxable PIR Instructions:

- Your name, field title and RDT
- The requesting HCP's full name and professional degree
- HCP's full mailing address
- HCP's phone number
- HCP's FAX number
- Provide the question(s) asked by the HCP.

PIR Requests may also be sent to Medical Services from 4:30 pm – 8:30am ET by leaving a voice message at 800MERCK66. The information as listed above should be provided in your voice message to Medical Services staff. Additionally, PIR requests may be submitted to Medical Services in writing by sending a fax to 800MERCK66. The information listed above should be included on your fax to Medical Services.

In Summary:

- If requested, a summary of the PIR will be faxed within 24 hours of receiving the request.
- If the physician requests more comprehensive information on the VIGOR study, you may request the comprehensive PIR. This will be sent via Fed EX within 2 days.
- Transition your discussion to the current strategy and messages for VIOXX®
- Do not proactively discuss the Advisory Committee Meeting or VIGOR. Respond to questions about the study by requesting a PIR and in accordance with the obstacle-handling guide.

Updated Q&A Guide:

This is background information only.

Exhibit A - Part 3

"VIGOR QA.doc"

Updated Obstacle Responses:

Obstacles.doc

These updated obstacles are provided for your reference and preparation for questions asked by your physicians.

This information is provided for your background information *only* and is not to be used in discussions with physicians.

Background Information:

Merck issued a press release summarizing the FDA Advisory Committee Meeting held on Feb 8. The press release is attached below for your background information only:

GAITHERSBURG, Md., Feb. 8, 2001 -- The Arthritis Advisory Committee of the Food and Drug Administration today reviewed Merck & Co., Inc.'s application for changes to the prescribing information for Vioxx® (rofecoxib), Merck's medicine for osteoarthritis and acute pain, to reflect results from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study.

The Advisory Committee agreed with Merck and the FDA that results from the study should be included in the labeling for Vioxx. The FDA is not obligated to follow the advice of the Advisory Committee, but usually does. The FDA noted that it will consider all available information, including the information reported and advice received at today's Advisory Committee meeting, before any final decisions are made on Merck's application and other issues discussed by the Committee.

"Merck is confident that the data presented today support the excellent safety profile of Vioxx, and we look forward to further discussions with the FDA to complete the review of our application to modify the labeling for Vioxx," said Eve Slater, M.D., senior vice president, Clinical and Regulatory Development, Merck Research Laboratories.

Vioxx was approved by the FDA in May 1999 to treat osteoarthritis and acute pain. The prescribing information for Vioxx currently contains the standard NSAID Warning about GI side effects. Merck's application to the FDA was based on the 8,000-patient VIGOR

study, which evaluated the GI profile of Vioxx 50 mg compared to the non-selective NSAID naproxen, and on other studies with Vioxx.

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Committee recommended that these results be included in the labeling. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

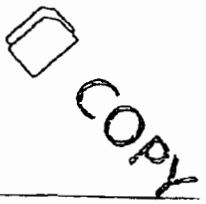
In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

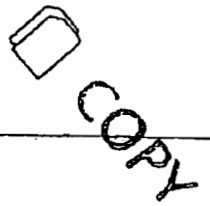
Focus:

Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute that physicians and patients are seeking is pain relief.



For questions regarding this bulletin please contact your Business Manager. For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).

Exhibit A - Part 3



Q&A-Field Personnel

FOR BACKGROUND USE ONLY
DO NOT DISCUSS WITH OR SHOW TO PHYSICIANS

Was there a relationship between hypertension and MI and stroke in VIGOR?

No. In VIGOR there was no correlation between hypertension adverse experiences and MI. Neither was there any difference in the incidence of stroke between patients taking VIOXX and naproxen.

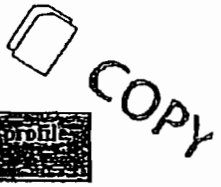
What was the incidence of stroke in VIGOR?

The rate of stroke was low and did not differ between the two groups.

Did you see edema and hypertension in the VIOXX GI Outcomes Study?

Yes. In VIGOR, the rates of edema and hypertension were consistent with what was seen in the Phase III trials that evaluated the chronic use of VIOXX 50 mg and what is in our current label. All NSAIDs work by inhibiting COX-2 and have effects on the kidney to some degree. These effects are understood to be mechanism-based and applicable to all NSAIDs. These effects were usually reversible upon discontinuation of therapy and only rarely resulted in patients' discontinuing from medication.

Exhibit A - Part 3



[redacted]

Clarify: Dr., specifically what safety concerns are you referring to?

If the physicians' concern is CV safety, refer to the updated obstacle #38 (below)

If the physicians' concern is GI safety, refer to obstacle # 26

For all other obstacle responses, please refer to your Reference Binder for VIOXX:
-If the physician's concern is related to concomitant use of VIOXX and low-dose aspirin, refer to **obstacle # 7**
-If the physician's concern is related to cardiovascular effects, such as MI's or the worsening of CHF, refer to **obstacle #23**
-If the physician's concern is related to renal effects or hypertension, refer to **obstacle #4 or #31.**

38. "I just read in the news that there is a concern about VIOXX and the incidence of heart attacks."

"Doctor, What you may be referring to is a press report addressing the VIOXX GI Outcomes Trial (VIGOR), reviewed at the FDA's Arthritis Advisory Committee Meeting. This was an 8000 patient study designed to evaluate the GI safety of VIOXX compared to the NSAID naproxen. All of the primary endpoints were met. However, because the study is not in the label, I cannot discuss the study with you. I would be happy to submit your question to our medical services department."

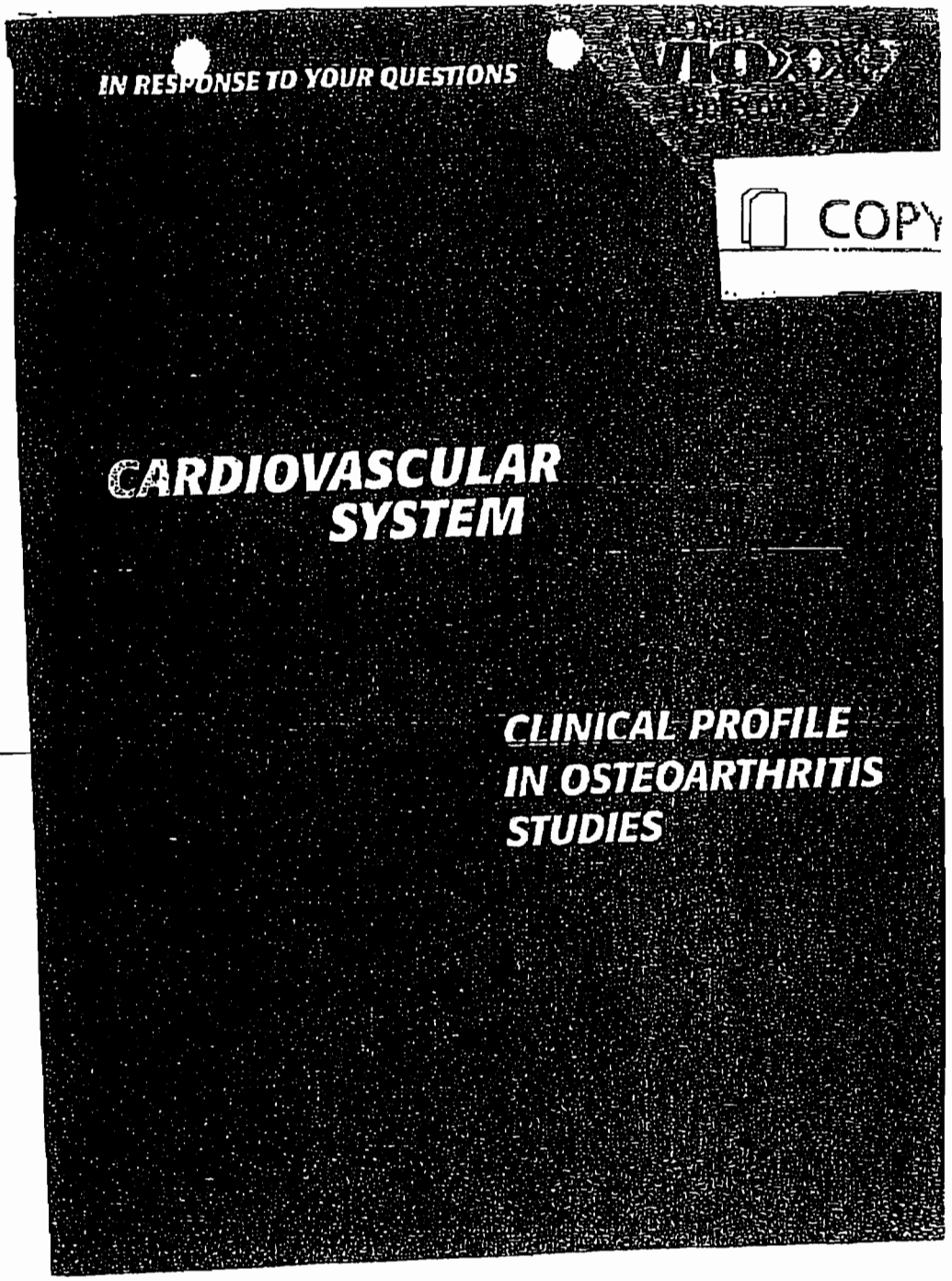
Note: You can also refer to the Cardiovascular System non-leave sales aid (OAN # 0013905) that reviews the cardiovascular profile of VIOXX as demonstrated in Phase IIb/III osteoarthritis studies. The results from VIGOR are <u>not</u> included in this piece.

7. Can VIOXX be used in patients using low dose aspirin?

There is no contraindication for concomitant use with low-dose aspirin.

Let me share with you the experience we have on the concomitant use of once daily VIOXX and low-dose aspirin. At steady state, once daily VIOXX 50mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX is not a substitute for aspirin for cardiovascular prophylaxis and the concomitant administration of low-dose aspirin with once daily VIOXX may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX alone.



MRK-ABR 001

Exhibit - Part a

PLAINTIFF'S EXHIBIT 6

CARDIOVASCULAR EVENT PROFILE

Cardiovascular thromboembolic adverse events in OA clinical trials[1]

- The overall incidence of cardiovascular thromboembolic adverse events was assessed. This review included events pertaining to cardiac (i.e., MI, angina), central nervous (i.e., CVA, TIA), and peripheral vascular (i.e., arterial embolism) systems.
- Due to the variable duration of treatment in the studies, results are expressed as events per 100 patient-years.

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years

	Placebo N=783	VIOXX 12.5 mg N=1,215	VIOXX 25 mg N=1,614	VIOXX* 50 mg N=526	Ibuprofen 2400 mg N=847	Diclofenac 150 mg N=590	Nabumetone 1500 mg N=128
Events**	2.9	3.2	2.6	3.3	2.6	3.1	3.9

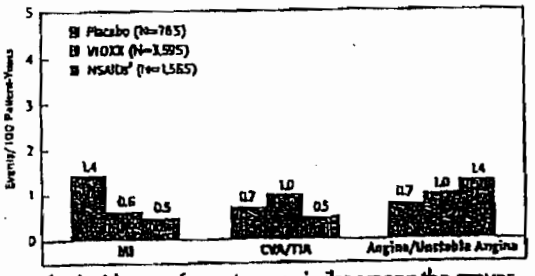
** MI, cerebrovascular accident (CVA), transient ischemic attack (TIA), and angina.

The incidence of events was similar among the groups.

*Recommended dosing in OA: The recommended dose of VIOXX is 12.5 mg once daily. Some patients may receive benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Specific cardiovascular thromboembolic events[1,3]

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years



‡Data are based on nine double-blind studies in approximately 6,000 OA patients actively taking VIOXX, active comparator, or placebo. Studies lasted from 6 weeks to a maximum duration of 86 weeks. The average duration of treatment was 5.5 months.

†NSAIDs are from OA clinical studies and include diclofenac 150 mg, ibuprofen 2400 mg, and nabumetone 1500 mg.

The incidence of events was similar among the groups.

Selected safety information

- As with all NSAIDs, VIOXX should be used with caution in patients with fluid retention, hypertension, or heart failure.
- Serious GI toxicity can occur with or without warning symptoms with NSAIDs.

IN OA STUDIES

BASELINE CARDIOVASCULAR (CV) CHARACTERISTICS[1]

CV Risk Factors	Percentage of Patients at Baseline*
Hypertension	39%
Hypercholesterolemia	11%
Current smoker	14%
Diabetes	7%
History of angina/coronary artery disease (CAD)	5%
History of myocardial infarction (MI)	3%
Congestive heart failure (CHF)	1%

*Mean age: 63 years (range: 39–93). Gender: 70% female, 30% male.

VIOXX is indicated for:

- Relief of the signs and symptoms of osteoarthritis (OA).
- The management of acute pain in adults (see CLINICAL STUDIES).
- Treatment of primary dysmenorrhea.

Selected safety information

- VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.
- VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Common adverse events included upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).
- Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.
- With NSAIDs, most spontaneous reports of fatal gastrointestinal (GI) events are in elderly or debilitated patients.
  —therefore, special care should be taken in treating these patients.

[redacted]

OA CLINICAL TRIALS

OVERALL MORTALITY RATES

Overall mortality and cardiovascular mortality*,†

Events per 100 Patient-Years

	VIOXX N=3,595	NSAIDs† N=1,565	Placebo N=783
Total mortality	0.1	1.1	0.0
Cardiovascular mortality	0.1	0.8	0.0

*Data are based on nine double-blind studies in approximately 6,000 OA patients actively taking VIOXX, active comparator, or placebo. Studies lasted from 6 weeks to a maximum duration of 86 weeks. The average duration of treatment was 5.5 months.

†NSAIDs are from OA clinical studies and include diclofenac 150 mg, ibuprofen 2400 mg, and nabumetone 1500 mg.

COX

Selected safety information

- VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.
- Concomitant administration of low-dose aspirin with VIOXX may result in an increased risk of GI ulceration or other complications compared with use of VIOXX alone.
- Drug-interaction studies with VIOXX have identified potentially significant interactions with warfarin. Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing therapy with VIOXX in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

ONCE DAILY

VIOXX®

(rofecoxib)

MRK-ABR 00125

Exhibit A - Part 3

VIOXX (rofecoxib)

TOLERABILITY PROFILE

Clinical adverse events in OA studies

Occurring in ≥2% of Patients Treated With VIOXX and >Placebo, Regardless of Causality*

Adverse Event	Once-Daily VIOXX 12.5 mg or 25 mg (N=2,829) %	Placebo (N=783) %	Ibuprofen 2400 mg daily (N=847) %	Diclofenac 150 mg daily (N=498) %
Fatigue	2.2	1.0	2.0	2.6
Dizziness	3.0	2.2	2.7	3.4
Lower extremity edema	3.7	1.1	3.8	3.4
Upper respiratory infection	8.5	7.8	5.8	8.2
Hypertension	3.5	1.3	3.0	1.6
Dyspepsia	3.5	2.7	4.7	4.0
Epigastric discomfort	3.8	2.8	9.2	5.4
Heartburn	4.2	3.6	5.2	4.6
Nausea	5.2	2.9	7.1	7.4
Sinusitis	2.7	2.0	1.8	2.4
Back pain	2.5	1.9	1.4	2.8
Bronchitis	2.0	0.8	1.4	3.2
Urinary tract infection	2.8	2.7	2.5	3.6

*Data are based on nine six-week to six-month clinical studies in OA patients taking VIOXX, active comparators, or placebo.

- In analgesia studies, the adverse-event profile of VIOXX 50 mg q.d. was generally similar to the adverse-event profile reported in the OA studies.
- In six-month OA studies using twice the maximum recommended dose, the general safety profile of VIOXX 50 mg q.d. was similar to that of VIOXX at recommended OA doses, except for a higher incidence of GI symptoms, lower extremity edema (6.3%), and hypertension (8.2%).
- The recommended doses for VIOXX in OA are 12.5 mg q.d. or 25 mg q.d.
- NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

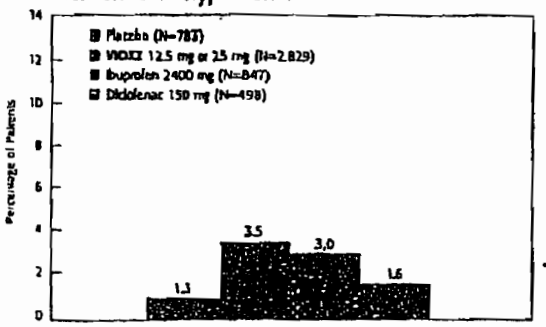
ADVERSE EVENTS PROFILE

VIOXX (rofecoxib)

Discontinuation rates for patients due to adverse events*,3

- Overall discontinuation rates due to any adverse event were low (6.7% for VIOXX 12.5 mg or 25 mg q.d. vs 4.2% for placebo).
- Low discontinuation rates for patients on VIOXX (12.5 mg or 25 mg q.d.) due to hypertension:
  - <0.1% of patients discontinued therapy due to hypertension

Incidence of hypertension*



*Data are based on nine double-blind six-week to six-month studies in approximately 6,000 OA patients taking VIOXX, active comparator, or placebo.

COPY

Selected safety information

- VIOXX is not recommended in patients with advanced kidney disease; no dosage adjustment is recommended in patients with mild to moderate kidney disease.
- Renal effects of VIOXX (e.g., hypertension, edema) were similar to those of comparator NSAIDs.
- Administration of NSAIDs has resulted in renal papillary necrosis and other renal injury, including acute renal failure.

Before prescribing VIOXX, please read the complete Prescribing Information.

References: 1. Daniels B, Seidenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials. Paper presented at: 1999 Annual Scientific Meetings; November 13–17; Boston, MA. *Arthritis Rheum.* 1999;42(9 suppl):S143. Abstract 435. 2. Data available on request from Professional Services, WP1-77, Merck & Co. Inc., West Point, PA 19486. Please specify information package DA-VIO14(1).

STRENGTH. SAFETY. QD SIMPLICITY.

www.vioxx.com

For use by Merck representatives only. Not to be left with healthcare professionals.

MRK-ABR 0012550

Exhibit A - Part 3

cor

John Q. Sample
Sample Medical Center
123 Sample St.Suite 100
Anywhere, US 12345

Rep Name
ROT #
P.O. Box 4
West Point, PA 19486-0004

Exhibit A-1 Part 3

PLAINTIFF'S EXHIBIT

COPY

Merck & Co., Inc.
P.O. Box 4
West Point, PA
19486-0004

John O. Sample MD
Sample Medical Center
123 Sample St.
Anywhere, US 12345

September 8, 2000

Dear Dr. Sample:

Thank you for taking a few moments from your busy schedule to discuss VIOXX® (rofecoxib) when I recently visited your office. As you recall, the strength, safety, and q.d. simplicity of VIOXX make it a powerful option for your patients who need:

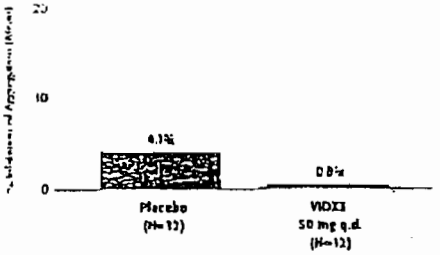
- Relief of the signs and symptoms of osteoarthritis (OA)
- Management of acute pain in adults (see CLINICAL STUDIES)
- Treatment of primary dysmenorrhea

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX. VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

VIOXX is *not a sulfonamide*; therefore, VIOXX has no sulfonamide contraindication.

VIOXX: No effect on platelet function in healthy volunteers
In healthy volunteers, VIOXX 50 mg had no effect on platelet aggregation.[1]

Effect on platelet aggregation[1]



Double blind, randomized, placebo-controlled, parallel-group study to assess the effect of VIOXX and placebo on platelets in healthy volunteers. In the two treatment groups (N=12/group), subjects received tablets of either 50 mg of VIOXX or matching placebo. Results shown are for Day 4.

Bleeding time: VIOXX at doses of up to 375 mg had no effect on bleeding time when administered daily for up to 12 days. Similarly, bleeding time was not altered with single doses of 500 mg or 1000 mg of VIOXX.

Low-dose aspirin: VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. At steady state, VIOXX 50 mg once daily had no effect on the antiplatelet activity of low-dose aspirin (81 mg once daily). Concomitant administration of low-dose aspirin with VIOXX may result in an increased risk of gastrointestinal (GI) ulceration or other complications compared with use of VIOXX alone.

Cardiovascular thromboembolic adverse events in OA clinical trials[1,2]
The overall incidence of cardiovascular thromboembolic adverse events was assessed. This review included events pertaining to cardiac (i.e., MI, angina), central nervous (i.e., CVA, TIA), and peripheral vascular (i.e., arterial embolism) systems. Due to the variable duration of treatment in the studies, results are expressed as events per 100 patient-years.

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Exhibit A - Part 3

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Exhibit A - Part 3

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West Point, PA
19486-0004

Cardiovascular Thromboembolic Adverse Events per 100 Patient-Years*,†

	Placebo N=783	VIOXX (rofecoxib) 12.5 mg N=1,215	VIOXX 25 mg N=1,614	VIOXX 50 mg N=526	Ibuprofen 2400 mg N=847	Diclofenac 150 mg N=590	Nabumetone 1500 mg N=176
Events‡	2.9	3.2	2.6	3.3	2.8	3.1	3.9

*Data are based on nine double-blind studies in approximately 6,000 OA patients actively taking VIOXX, active comparator, or placebo. Studies lasted from 6 weeks to a maximum duration of 80 weeks. The average duration of treatment was 5.5 months.

†Myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), and angina.

‡The incidence of events was similar among the groups.

**Recommended dosing in OA: The recommended dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

In acute pain and primary dysmenorrhea, 50 mg once daily is the recommended initial dose. Subsequent doses of 50 mg may be used as needed. Use of VIOXX for more than five days in the management of acute pain has not been studied.

Selected safety information
Serious GI toxicity can occur with or without warning symptoms with NSAIDs.

Serious renal and hepatic reactions have been reported with NSAID use. VIOXX is not recommended in patients with moderate or severe hepatic insufficiency or in patients with advanced kidney disease. As with all NSAIDs, VIOXX should be used with caution in patients with fluid retention, hypertension, or heart failure.

Common adverse events in OA studies of six weeks' to six months' duration included upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).

In analgesia studies, the adverse-event profile of VIOXX 50 mg once daily was generally similar to the adverse-event profile reported in the OA studies.

In six-month OA studies using twice the maximum recommended dose for OA, the general safety profile of VIOXX 50 mg once daily was similar to that of VIOXX at recommended OA doses, except for a higher incidence of GI symptoms, lower extremity edema (6.2%), and hypertension (8.2%).

Before prescribing VIOXX, please read the enclosed complete Prescribing Information.

Sincerely,

John Q. Sample

John Q. Sample

P.S. Please consider VIOXX for your adult patients who need relief from the signs and symptoms of chronic OA, management of acute pain, or treatment of primary dysmenorrhea. I look forward to meeting with you again to further discuss VIOXX.

References: 1. Data available on request from Professional Services, WP1-27, Merck & Co., Inc., West Point, PA 19486. Please specify Information package DA-VIO1(1). 2. Daniels B, Settenberg B. Cardiovascular safety profile of rofecoxib in controlled clinical trials. Paper presented at: 1999 Annual Scientific Meetings; November 13–17; Boston, MA. Arthritis Rheum. 1999;42(9 suppl):S143. Abstract 435.

VIO01(A)

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035708(1)-05-VIO

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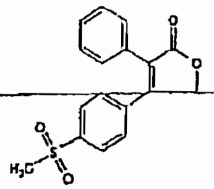
Exhibit A - Part 3

VIOXX®
(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX* (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone. It has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$ and the molecular weight is 314.36.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The AUC_{0-24hr} and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/mL. The apparent volume of distribution at steady state (V_{dss}) is approximately 91 L following a 12.5-mg dose and 86 L following a 25-mg dose.

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the cis-dihydro and trans-dihydro derivatives of rofecoxib which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as

the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (≤5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non-specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations. (Also see *Drug Interactions*.)

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

Pediatric

VIOXX has not been investigated in patients below 18 years of age.

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. Limited data in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency suggest a trend towards higher AUC (about 69%) of rofecoxib in these patients, but more data are needed to evaluate pharmacokinetics in these patients. Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX in these patients.

Drug Interactions (Also see PRECAUTIONS, *Drug Interactions*.)

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. In vitro studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with rofecoxib have identified potentially significant interactions with rifampin, methotrexate and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six stud-

ies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies); this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional arthritis medication during the last 6 months.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Special Studies

Upper Endoscopy in Patients with Osteoarthritis

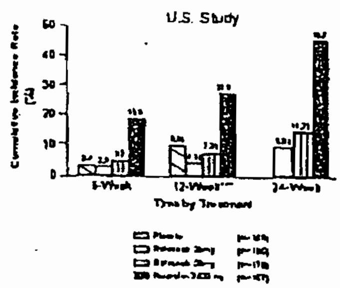
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo. See Figures 1 and 2 and the accompanying tables for the results of these studies.

Figure 1

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm** (Intention-to-Treat)



* p < 0.001 versus ibuprofen 2400 mg

** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

TABLE 1
Incidence of Gastroduodenal Ulcers at 12 weeks
U.S. Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	[illegible]	9.9%	-	-
VIOXX 25 mg	[illegible]	4.1%	[illegible]	[illegible]
VIOXX 50 mg	[illegible]	7.3%	[illegible]	[illegible]
Ibuprofen	[illegible]	27.7%	[illegible]	[illegible]

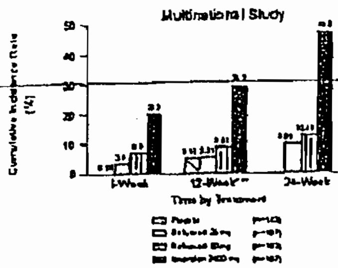
* by life table analysis

*Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3mm** (Intention-to-Treat)



* p ≤ 0.001 versus Ibuprofen 2400 mg

** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.

*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

TABLE 3

Endoscopic Gastroduodenal Ulcers at 12 weeks

Multinational Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	[illegible]	[illegible]	–	–
VIOXX 25 mg	[illegible]	[illegible]	[illegible]	[illegible]
VIOXX 50 mg	[illegible]	[illegible]	[illegible]	[illegible]
Ibuprofen	[illegible]	[illegible]	[illegible]	[illegible]

* by life table analysis

The correlation between findings of endoscopic studies and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently (see WARNINGS, Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX versus comparator NSAID products have not been performed.

Assessment of Fecal Occult Blood Loss In Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX 25 mg daily or VIOXX 50 mg daily, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

Multiple doses of VIOXX 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000 mg of VIOXX. There was no inhibition of ex vivo arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

INDICATIONS AND USAGE

VIOXX is indicated:

For relief of the signs and symptoms of osteoarthritis.

For the management of acute pain in adults (see CLINICAL STUDIES).

For the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX.

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis*). Among 3357 patients who received VIOXX in controlled clinical trials of 6-weeks to one-year duration (most were enrolled in six-month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol-derived criteria. Two patients experienced an upper GI bleed within three months (at day 62 and 87, respectively) (0.06%). One additional patient experienced an obstruction within six months (Day 130) and the remaining patient developed an upper GI bleed within 12 months (Day 322) (0.12%). Approximately 23% of these 3357 patients were in studies that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population. To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX. In post-marketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving VIOXX. VIOXX should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal Effects*).

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

PRECAUTIONS

General

VIOXX cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Hepatic Effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency (see *Pharmacokinetics, Special Populations*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Renal Effects

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS.)

Caution should be used when initiating treatment with VIOXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, *Advanced Renal Disease*).

Hematological Effects

Anemia is sometimes seen in patients receiving VIOXX. In placebo-controlled trials, there were no significant differences observed between VIOXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see CLINICAL STUDIES, *Special Studies, Platelets*).

Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

Preexisting Asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, VIOXX should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Information for Patients

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation*).

Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema to their physicians.

MRK-ABR 0004076

Exhibit A - Part 3

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.

Drug Interactions

ACE inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of Angiotensin Converting Enzyme (ACE) inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Aspirin: Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB_2 generation in clotting blood. VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.

Cimetidine: Co-administration with high doses of cimetidine (800 mg twice daily) increased the C_{max} of rofecoxib by 21%, the $AUC_{0-120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

Furosemide: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by AUC_{0-24hr} in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in methotrexate renal clearance was observed. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). The effects of the recommended doses for osteoarthritis (12.5 and 25 mg) of VIOXX on plasma methotrexate levels are unknown. Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on AUC_{0-24}) for two years.

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an in vitro and an in vivo alkaline elution assay, or in an in vivo chromosomal aberration test in mouse bone marrow.

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the AUC_{0-24}) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}).

Pregnancy

Teratogenic effects: Pregnancy Category C.

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the Pregnancy Registry at (800) 986-8999.

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older). No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

In one of these studies (a six-week, double-blind, randomized clinical trial), VIOXX 12.5 or 25 mg once daily was administered to 174 osteoarthritis patients ≥80 years of age. The safety profile in this elderly population was similar to that of younger patients treated with VIOXX.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences occurring in ≥2.0% of Patients Treated with VIOXX	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

The general safety profile of VIOXX 50 mg QD in OA clinical trials of up to 6 months (470 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 and 25 mg QD, except for a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema (6.3%) and hypertension (8.2%).

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heart beat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysphagia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, hypersensitivity, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric: anxiety, depression, mental acuity decreased.

Exhibit A - Part 3

VIOXX® (rofecoxib tablets and oral suspension)

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, bullae, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail bed disorder, perspiration, pruritus, rash, skin carcinoma, sutures, uremia.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported spontaneously in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in bold.

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, duodenal perforation, duodenal ulcer, esophageal ulcer, gastric perforation, gastric ulcer, pancreatitis, gi bleeding, intestinal obstruction, pancreatitis.

Hemic and lymphatic: hemolysis.

Immune System: anaphylaxis reaction, angioedema

Nervous System: aseptic meningitis

Psychiatric: hallucinations

Urogenital System: acute renal failure, breast malignant neoplasm, interstitial nephritis, prostatic malignant neoplasm, proteinuria, worsening chronic renal failure.

In 1-year controlled clinical trials and in extension studies for up to 68 weeks (approximately 800 patients treated with VIOXX for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Analgesia, including primary dysmenorrhea

Approximately one thousand patients were treated with VIOXX in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX, and those in the post-orthopaedic surgery pain study were prescribed 5 daily doses of VIOXX.

VIOXX® (rofecoxib tablets and oral suspension)

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX, was observed in the post-dental pain surgery studies: post-dental procedure alveolitis (dry socket).

In 118 patients treated with VIOXX (average age approximately 65 years) in the post-orthopaedic surgery pain study, the most commonly reported adverse experiences were constipation, fever, and nausea.

OVERDOSAGE

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not removed by hemodialysis; it is not known whether rofecoxib is removed by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

Osteoarthritis

The recommended starting dose of VIOXX is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of pain has not been studied (see CLINICAL STUDIES, Analgesia, *including dysmenorrhea*).

VIOXX tablets may be taken with or without food.

Oral Suspension

VIOXX Oral Suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX Tablets 12.5 or 25 mg, respectively, in any of the above indications. Shake before using.

VIOXX® (rofecoxib tablets and oral suspension)

HOW SUPPLIED

No. 3810 - Tablets VIOXX, 12.5 mg, are claret/M-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-58 bottles of 500
NDC 0006-0074-52 bottles of 1000
NDC 0006-0074-68 bottles of 5000.

No. 3811 - Tablets VIOXX, 25 mg, are yellow, round, tablets engraved MRK 118 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0118-31 unit of use bottles of 30
NDC 0006-0118-28 unit dose packages of 100
NDC 0006-0118-58 bottles of 100
NDC 0006-0118-52 bottles of 1000
NDC 0006-0118-68 bottles of 5000.

No. 3813 — Tablets VIOXX, 50 mg, are orange, round, tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-58 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-68 bottles of 4000.

No. 3784 - Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is readily resuspended upon shaking.

NDC 0006-3784-44 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 - Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is readily resuspended upon shaking.

NDC 0006-3785-54 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage

VIOXX Tablets:

Store at 25°C (77°F); excursions permitted to 15-30°C [59-86°F]. [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F); excursions permitted to 15-30°C [59-86°F]. [See USP Controlled Room Temperature.]

Rx only

Issued March 2000
Printed in USA

MRK-ABR 0004078

Exhibit A - Part 3

No. COX 01-030
May 23, 2001

COPY

Bulletin for VIOXX®:
Action Required: Response to New York Times Article

TO:

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
Neurology Representatives	Action Required
Managed Care NAEs and Customer Managers (all segments)	Background Information

DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY, OR ANY OF THE RECENT ARTICLES IN THE PRESS ON VIOXX. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.

PURPOSE:

To provide you with important background information, obstacle responses and faxable PIR instructions in the event that you are questioned by customers about the CV effects of VIOXX.

ACTIONS REQUIRED:
Obstacle Response #38: (originally issued in Bulletin COX 00-029)

[redacted]

"Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.5% with VIOXX and 0.1% with naproxen. In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations."

If the doctor asks you further for the incidence of MI from the OA studies presented in the ~~package insert for VIOXX tell them:~~

PLAINTIFF'S EXHIBIT

Exhibit 4 - Part 8

"In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX."

Use your CV Card to show the data on studies involving VIOXX and various NSAIDs (ibuprofen, diclofenac, and nabumetone) on overall mortality and CV mortality rates

"Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was **VIOXX .1 vs. NSAIDs .8 vs. Placebo 0."**

Physician Inquiries:

In response to unsolicited requests for information regarding the recent press releases, Medical Services will make a personalized, faxable PIR available for your customers within 24 hours. In addition, for those customers who request more detailed information, a separate, more comprehensive PIR packet can be Federal Expressed within 2 days.

Medical Services has made arrangements to extend the hours for the PIR hotline. Representatives should submit unsolicited PIR requests by either telephone or fax options by calling the PIR hotline **800MERCK66** (800-637-2566) during extended hours of **8:30 am to 6:30pm ET**. During these hours, a staff member will verbally request the following information from you to process the PIR request from the HCP [After this time, the usual method options of INSIGHT, PIR hotline (800MERCK 66 -- hours: 8:30 -- 4:30pm ET) and fax can be followed].

Faxable PIR Instructions:

- Your name, field title and RDT
- The requesting HCP's full name and professional degree
- HCP's full mailing address
- HCP's phone number
- HCP's FAX number
- Provide the question(s) asked by the HCP.

PIR Requests may also be sent to Medical Services from 4:30 pm – 8:30am ET by leaving a voice message at 800MERCK66. The information as listed above should be provided in your voice message to Medical Services staff. Additionally, PIR requests may be submitted to Medical Services in writing by sending a fax to 800MERCk68. The information listed above should be included on your fax to Medical Services.

- If requested, a PIR will be faxed within 24 hours of receiving the request.
- If the physician requests more comprehensive information on the cardiovascular safety profile of VIOXX, you may request the comprehensive PIR. This will be sent via Fed EX within 2 days.
- Transition your discussion to the current strategy and messages for VIOXX®.

Do not proactively discuss any of the recent press stories. Respond to questions by requesting a PIR and in accordance with the obstacle-handling guide.

This information is provided for your background information *only* and is not to be used in discussions with physicians. The following press release was issued in response to an article in Tuesday's New York Times on the cardiovascular effects of VIOXX.

Background Information:

Tuesday May 22, 1:21 pm Eastern Time

Press Release

SOURCE: Merck & Co., Inc.

Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx(R)

UPPER GWYNEDD, Pa., May 22 /PRNewswire/ – In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in The New England Journal of Medicine and discussed extensively by an FDA Advisory Committee.

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

Focus:
Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute for physicians and patients is pain relief.

Exhibit A - Part 3

No. COX 01-031
May 24, 2001

COPY

Bulletin for VIOXX®:
Action Required: REVISED Response to New York Times Article

TO:

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
Neurology Representatives	Action Required
Managed Care NAEs and Customer Managers (all segments)	Background Information

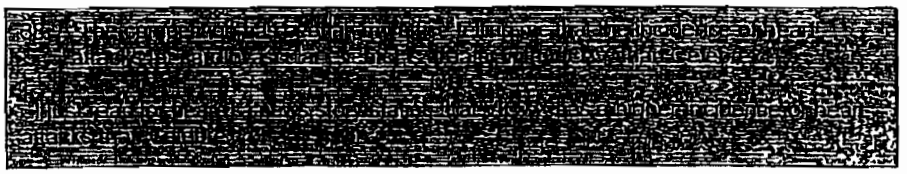
DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY, OR ANY OF THE RECENT ARTICLES IN THE PRESS ON VIOXX. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.

PURPOSE:

To provide you with important background information, obstacle responses and faxable PIR instructions in the event that you are questioned by customers about the CV effects of VIOXX.

ACTIONS REQUIRED:

Obstacle Response #38: (originally issued in Bulletin COX 00-029)



"Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.5% with VIOXX and 0.1% with naproxen. In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations."

Exhibit A - Page 3

PLAINTIFF'S EXHIBIT
Barkin

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them:

"In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX."

Use your CV Card to show the data on studies involving VIOXX and various NSAIDs (ibuprofen, diclofenac, and nabumetone) on overall mortality and CV mortality rates

"Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was VIOXX .1 vs. NSAIDs .8 vs. Placebo 0."

Physician Inquiries:

Reminder: In accordance with policy letters 110, 118, and 131, Field Personnel, including Professional Representatives, HSAs, Hospital Tablet Representatives, Specialty Representatives and NAEs may not discuss off-label information about VIOXX with health care professionals (HCP). In accordance with policy letter 104A, Field Personnel may submit PIRs to Medical Services when an HCP has an unsolicited request for information.

PURPOSE:
To provide you with toll free phone numbers for the one Fax PIR available from Medical Services in response to unsolicited requests for information from HCPs regarding VIOXX and Response to media reports about cardiovascular adverse events.

ACTION REQUIRED:
In response to unsolicited questions from HCPs, you may request PIRs from Medical Services by using EITHER the interactive voice response (IVR) same day fax service, or by using the usual PIR request methods as stated in policy 104A. PIRs requested via the IVR same day fax service will be provided as a "nonpersonalized" Dear Doctor Letter. Specific steps for using the IVR fax service are outlined below.

OVERVIEW:
1. IVR FAX METHOD –
Effective Thursday 5/24 3 pm ET, through close of business Friday, June 29, 2001 (excluding holidays), Medical Services will have one PIR available via fax to respond to the following type of inquiry:

- Fax = VIOXX and Response to Media Reports about Cardiovascular Adverse Events

In response to unsolicited questions about the above topics, the PIR – VIOXX and Response to Media Reports about Cardiovascular Adverse Events will be available from Medical Services via the interactive voice response (IVR) same day fax service and provided as a "nonpersonalized" Dear Doctor Letter.

Exhibit A - Part 3

Toll Free Fax PIR Request Telephone Number:

You may submit a HCPs request for a faxed PIR(s) by simply calling 1-877-372-7064 .

- This toll free phone number will be made available from 8:00am – 10:00pm (ET). Since this line is an IVR system, a touch tone phone must be used in order to provide the pertinent information needed as prompted in the system.

Please follow the detailed instructions outlined below for requesting the faxable "nonpersonalized" Dear Doctor Letter.

You should be prepared to provide the following pertinent information as prompted by the system:

- Your Region, District, and Territory identifier
- Requesting Physician's 5 digit ZIP code
- Requesting Physician's full name and professional degree (speak)
- Requesting Physician's full mailing U.S. address (speak)
- Requesting Physician's phone number with area code
- Requesting Physician's FAX number with area code

Select the faxes requested by the physician:

- **FAX = VIOXX and Response to Media Reports about Cardiovascular Adverse Events**

IMPORTANT NOTE: PIRs ARE NOT TO BE REPRODUCED IN ANY FORM!

This one fax will be sent directly to the requesting physician's office as "nonpersonalized" Dear Doctor Letter. This fax should arrive as soon as 15 minutes from the time of the request. You must leave a copy of the circular for VIOXX with the HCP. (Note: For pharmacists, nurses, and physician assistants, you may also want to send the 'Dear Doctor' letter.)

You also have the option to follow the usual procedure established for processing a PIR using the methods through Medical Services as stated in Policy 104A.

Toll Free IVR HELPLINE Telephone Number:
If you experience difficulty with the IVR system or if there is difficulty receiving the fax, representatives should call the IVR HELPLINE at 1-888-721-7204 (9:00 am to 7:00 pm ET)

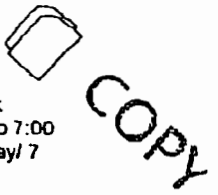
- This number will be on the cover sheet of both faxes available to the physician.
- This number is staffed from 9:00 am to 7:00 pm ET.

2. ADDITIONAL OTHER PIRS FOR VIOXX ARE AVAILABLE FROM MEDICAL SERVICES IN RESPONSE TO UNSOLICITED INQUIRIES FROM HCPS BY USING THE USUAL METHODS TO SUBMIT PIRS AS STATED IN POLICY LETTER 104A.

The usual PIR request methods are (note: choose only one method for each request):

- INSIGHT and processing using the PIR screen;
- PIR hotline at 800-MERCK66 (8:30 am to 6:30 pm ET as extended hours) in Medical Services. This phone number is NOT to be given to an HCP, but is for Merck Field Personnel use only to verbally submit the questions asked by HCPs. PIR inquiries may be submitted to Medical Services 24 hours a day, 7 days a week with voice message available after hours (6:30pm to 8:30am ET).
- Faxing your request to Medical Services at 800-MERCK68.

Exhibit A - Part 3



If a health care provider requests to speak with a Merck health care professiona , the Merck National Service Center should be called at 800-NSCMERCK (business hours of 8:00 am to 7:00 pm ET; For emergency issues, Medical Services after-hours Call Coverage is 24 hours a day/ 7 days a week.)

Remember to always provide a balanced discussion consistent with the health care provider's knowledge of the product and the product prescribing information.
Please continue to provide competitive and promotional feedback to the National Service Center (NSC). The NSC is staffed Monday through Friday, 8:00am to 7:00pm Eastern Time. Please contact the NSC at 1-800-NSC-MERCK or 1-800-672-6372.

For product and service information, call the Merck National Service Center at 1-800-NSC-Merck (1-800-672-6372).

Do not proactively discuss any of the recent press stories. Respond to questions by requesting a PIR and in accordance with the obstacle-handling guide.

This information is provided for your background information *only* and is not to be used in discussions with physicians. The following press release was issued in response to an article in Tuesday's New York Times on the cardiovascular effects of VIOXX.

Background Information:

Tuesday May 22, 1:21 pm Eastern Time

Press Release

SOURCE: Merck & Co., Inc.

Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx(R)

UPPER GWYNEDD, Pa., May 22 /PRNewswire/ -- In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in The New England Journal of Medicine and discussed extensively by an FDA Advisory Committee.

Exhibit A - Part 3

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

Focus:
Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute for physicians and patients is pain relief.

For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).

Exhibit A - Part 3

COPY

No. COX 99-033
Jun 03, 1999

Field Incentive Plan for VIOXX®

TO:
Group 4-6 Representatives — Background Information Only
Group B Business Managers — Background Information Only

PURPOSE:

To review the existing field incentive plan for VIOXX® with you as well as announce an additional launch incentive for VIOXX®.

OVERVIEW:

You have three incentive opportunities for VIOXX®:
(1) Traditional in-line monetary incentive program
(2) Non-monetary incentive program (aka "003: License to Sell")
(3) And now an additional launch incentive program

In-Line Monetary Incentive Program:

The in-line bonus is fairly equally weighted between VIOXX®, SINGULAIR® and FOSAMAX®. Our goal with VIOXX® is to be the market leader in the market leading class. While there is no doubt that taking share away from Celebrex may be our sweetest victory, we should not limit ourselves to Celebrex. To become a true market leader, we're also going to have to focus our attention on traditional NSAIDS as well as new patient starts. You have a tremendous opportunity with VIOXX®; over plan performance will add substantially to your in-line product bonus pay out.

Non-Monetary Incentive Program (NMIP):

We are pleased to rollout the NMIP for VIOXX® to you. You will have the opportunity to earn the following NMIP AwardperQs moving forward:

- Approximately 1200 AwardperQs can be earned based on your performance at the National Launch Meeting.
- Future AwardperQs may be earned based on your market share performance with VIOXX® following launch.

Additionally, you have an opportunity to win a trip to the Caribbean aboard the cruise ship the Grand Princess, the largest, most expensive cruise ship ever built. If you and your Group B clustermates finish as the top cluster within your Region based on market share performance with VIOXX®, you can earn yourselves a spot on this "Top Performer Trip."

Please refer to VIOXX® bulletin COX99021 sent out on May 26 and the 003: License to Sell website on the FSNet for additional details on the program.

Additional Launch Incentive Program:

Exhibit R - Part 3

PLAINTIFF'S EXHIBIT R

This is a group monetary incentive driven off market share with a cash payout. To qualify for the incentive, you must achieve 51 percent share of new prescriptions in the C2-SI market for one month by March of 2000 and maintain activity and performance levels for your other key brands during the launch period for VIOXX®. Achieve these goals, and you'll receive a $2000 bonus on top of all other incentives. This bonus will be paid out to all members of the cluster (Groups I - VI) in the month following the month you achieve 51 percent share .

IF YOU HAVE ANY QUESTIONS ABOUT THIS BULLETIN, PLEASE CONTACT THE MERCK NATIONAL SERVICE CENTER AT 1-800-NSC-MERCK.

COPY

No. COX 99-034
Jun 04, 1999

Field Incentive Plan for VIOXX®

TO:

Group 1-3 Representatives	Background Information Only
Hospital Representatives	Background Information Only
A&A Specialists	Background Information Only
Group A Business Managers	Background Information Only
Hospital Managers	Background Information Only
A&A Specialty Managers	Background Information Only

PURPOSE:

To announce an additional launch incentive for VIOXX® available to you.

OVERVIEW:

An additional launch incentive program is now available to you. This is a group monetary incentive driven off market share with a cash payout. To qualify for the incentive you must achieve 51 percent share of new prescriptions in the C2-SI market for one month by March of 2000 and maintain activity and performance levels for your other key brands. Achieve these goals, and you'll receive a $2000 bonus on top of all other incentives. This bonus will be paid out to all members of the cluster (Groups 1 – 6) in the month following the month you earn it.

Your management team will review this program with you at your upcoming District Launch Meeting.

IF YOU HAVE ANY QUESTIONS ABOUT THIS BULLETIN, PLEASE CONTACT THE MERCK NATIONAL SERVICE CENTER AT 1-800-NSC-MERCK.

PLAINTIFF'S EXHIBIT

Exhibit A - Part 3

COPY

No. COX 99-035
Jun 08, 1999

Promotional Resources for VIOXX®

TO:

Group 1 – 6 Representatives	Action Required
Hospital Representatives	Action Required
A&A Specialists	Action Required
Long Term Care Specialists	Action Required
Kaiser Specialists	Action Required

PURPOSE:

To support your resource needs for VIOXX®in the coming weeks, beginning the week of June 7 and extending through mid-July, you will receive direct shipments of promotional resources to use in discussions on VIOXX® with your physicians.

OVERVIEW:

Promotional Resources being direct shipped:
⇒ Annotated PIs (9915211)
⇒ Branded Pens (995332)
⇒ Branded Sticky Pads (9947131)
⇒ PI Fold-Out Cards (991529)

Delivery Schedule and Contents:
⇒ Week of June 7:
- Groups 4-6 Representatives, Hospital Specialty Tablet Representatives and A&A Specialists will receive a supply of branded pens, branded sticky pads and annotated PIs,
- Group 1-3 Representatives, Hospital CV Tablet Representatives, Acute Care Representatives, Long Term Care Representatives and Kaiser Representatives will receive a supply of annotated PIs

⇒ Weeks of June 14, June 23, June 30:
- Group 1-6 Representatives, Hospital Specialty and CV Tablet Representatives, Acute Care Specialists, A&A Specialists, Long Term Care Specialists, Kaiser Specialists will receive a supply of branded pens, branded sticky pads and PI Fold-Out Cards*

*Note: PI Fold-Out Cards will be shipped as soon as available, possibly as early as June 14

⇒ Mid-July:
- Group 1-6 Representatives, Hospital Table Specialists, Acute Care Specialists, A&A Specialists, Long Term Care Specialists, Kaiser Specialists will receive a supply of branded pens, branded sticky pads and PI Fold-Out Cards

ACTION REQUIRED:

Early this week you received an initial supply of the annotated PIs for VIOXX®. The week of June 7, you will receive your second and final supply of the annotated PIs for VIOXX®. Over the next few weeks, you should use this piece in all your discussions on VIOXX® with physicians. Please remember, however, that by next week you will have received your entire supply of annotated PIs. Therefore it is important that you work with your clustermates to effectively manage this resource and selectively leave this piece with physicians.

Exhibit A - Part 3